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SULFOLANE

Introduction

Sulfolane, tetrahydrothiophene-1,1-dioxide, is a man-made industrial solvent commonly used in gas production and oil refining (Alaska Department of Health and Social Services [ADHSS] 2012). The sulfur-oxygen double bond is highly polar, which makes it very water soluble. The presence of the four-carbon ring allows for some non-polar stability. These properties make sulfolane miscible in both water and hydrocarbons, which gives it desirable properties as a solvent for purifying hydrocarbon mixtures (ADHSS 2012).

Sulfolane is absorbed via the oral route. However, is not readily absorbed via the dermal and inhalation routes. Animal studies have shown that sulfolane is not readily absorbed through human skin because of its low permeability (Brown et al. 1966) and is not expected to pose a significant risk via an inhalation exposure route due to its low volatility (Andersen et al. 1977). Brown et al. (1966) studied the skin and eye irritant and skin sensitizing properties of acute exposures to sulfolane on two animal species. It was concluded that sulfolane did not irritate or sensitize the skins of guinea pigs or rabbits and, undiluted, was only very mildly irritating on the eyes of rabbits. Andersen et al. (1977) conducted acute and subacute investigations of the inhalation toxicity of sulfolane on four animal species including monkey, dog, guinea pig and rat. A no observed adverse effect level (NOAEL) of 20 mg sulfolane per cubic meter (m^3) was reported. The authors also concluded that airborne concentrations of sulfolane as high as those investigated are unlikely to be encountered on any but an emergency basis. They reported that sulfolane has a relatively low vapor pressure of about 0.13 millimeters mercury at 32° Celsius and that only unusual conditions would produce extensive release of aerosolized sulfolane. They further noted that if it is handled at room temperature in an area with proper ventilation, sulfolane should not be regarded as posing any unusual hazard.

There are three laboratory animal studies that have been used by various parties to derive toxicological reference values for sulfolane. Zhu et al. (1987) was a six-page report published in a Chinese journal entitled Huaxi yike daxue xuebao, (Journal of West China University of Medical Sciences). In this study, a series of experiments were performed. Acute, subchronic (90-day), and chronic (6-month) toxicity testing was performed via the oral route of exposure in mice, white rats, and guinea pigs. Zhu et al. (1987) also performed a developmental toxicity study in mice and several genotoxicity tests. Huntingdon Life Sciences (2001) was a GLP-compliant study in which sulfolane was administered to CD rats (10/sex/group) in drinking water at concentrations of 0, 25, 100, 400, or 1600 mg/L for 13 weeks. All animals were examined for individual signs of general health, body weights, food and water consumption, ophthalmoscopy, functional observation battery, hematology, blood chemistry, organ weights, macropathology, and hisopathology. The Ministry of Health and Welfare Japan (MHWJ, 1999) was a 50-day oral gavage study in Crj:CD(S-D) rats as summarized in Organization for Economic Co-operation and Development ([OECD] 2004). These studies are evaluated below in the context of evaluating existing Reference Doses (RfDs) and similar toxicological reference criteria and deriving the alternative scientifically defensible RfDs from the scientific literature.

These studies have been evaluated in various efforts to set toxicologic criteria by U.S and Canadian entities and by ATSDR and form the basis for the EPA's PPRTV. They are also considered in the attached Assessment of Dose Response for Sufolane by Dr. Brian Magee of Arcadis.

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ARCADIS

ARCADIS U.S., Inc.
1 Executive Drive
Suite 303
Chelmsford
Massachusetts 01824
Tel 978 937 9999
Fax 978 937 7555

MEMO

To:
Flint Hills Resources Alaska

Copies:

From:
Brian Magee, Ph.D. Vice President, Principal Toxicologist

Date:
May 21, 2012

ARCADIS Project No.:
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Subject:
ASSESSMENT OF DOSE RESPONSE INFORMATION FOR SULFOLANE

There are three laboratory animal studies that have been used by various parties to derive toxicological reference values for sulfolane. Zhu et al. (1987) was a six-page report published in a Chinese journal entitled Huaxi yike daxue xuebao, (Journal of West China University of Medical Sciences). In this study, a series of experiments were performed. Acute, subchronic (90-day), and chronic (6-month) toxicity testing was performed via the oral route of exposure in mice, white rats, and guinea pigs. Zhu et al. (1987) also performed a developmental toxicity study in mice and several genotoxicity tests. Huntingdon Life Sciences (2001) was a GLP-compliant study in which sulfolane was administered to CD rats (10/sex/group) in drinking water at concentrations of 0, 25, 100, 400, or 1600 mg/L for 13 weeks. All animals were examined for individual signs of general health, body weights, food and water consumption, ophthalmoscopy, functional observation battery, hematology, blood chemistry, organ weights, macropathology, and hisopathology. The Ministry of Health and Welfare Japan (MHWJ, 1999) was a 50-day oral gavage study in Crj:CD(S-D) rats as summarized in Organization for Economic Co-operation and Development ([OECD] 2004). These studies are evaluated below in the context of evaluating existing Reference Doses (RfDs) and similar toxicological reference criteria and deriving the alternative scientifically defensible RfDs from the scientific literature.

Summary of Alternative Scientifically Defensible Reference Doses

ARCADIS, U.S., Inc. (ARCADIS) scientifically evaluated the existing RfDs and equivalent toxicological reference values and found that all existing values had issues that did not allow ARCADIS to endorse any of them. Accordingly, ARCADIS derived chronic and subchronic RfDs in accordance with the best available science and United States Environmental Protection Agency (USEPA) guidance for evaluation of

primary toxicology studies and the derivation of RfDs. The alternative scientifically defensible RfDs are as follows:

Chronic RfD 0.01 mg/kg-day

Subchronic RfD 0.1 mg/kg-day

According to the USEPA, a chronic RfD is: "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, lowest observed adverse effects level (LOAEL), or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments" (USEPA 2011).

Similarly, according to USEPA, a subchronic RfD is: "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a subchronic duration (up to 10% of average lifespan) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments" (USEPA, 2011).

Accordingly, a subchronic RfD is applicable for human health risk assessments involving exposure durations of up to 7 years, which is 10% of an average human lifetime of 70 years. A chronic RfD is applicable for risk assessments involving exposures that exceed 7 years in duration.

USEPA and certain regulatory agencies derive RfDs, not the Agency for Toxic Substances and Disease Registry (ATSDR). Instead, ATSDR derived "public health action levels" for sulfolane using similar procedures as USEPA uses to derive RfDs. The difference between USEPA and ATSDR actions is that USEPA RfDs and State regulatory agency RfDs are toxicological reference values that have regulatory standing and must be used to assess human health risks when performing site specific risk assessments. ATSDR's public action levels no not have regulatory standing as noted in ATSDR documents.

"The public health action level is a non-regulatory level set to identify if human exposure to that water needs to be evaluated further (a/k/a, a screening level). If exposure is occurring, then consideration should be given to reducing that exposure." (ATSDR 2010)

"The public health action level is a non-regulatory level set to identify whether human exposure needs further evaluation." (ATSDR 2011)

"A public health action level is a recommended, but not required (i.e., non-regulatory), level above which a public health intervention might be needed. Public health interventions are actions taken to reduce further chemical exposure, such as switching to another drinking water source. An action level can be used as a screening tool, because water concentrations of a chemical (contaminant) below that amount do not pose a public health concern." (ADHSS 2012)

"The ATSDR action level is a screening level, and not a clear line between safe and unsafe. It is used as a first step to identify potential contaminants of public health importance for further detailed evaluation, and is therefore set approximately 1,000 times lower than levels that caused health effects in animals. (ADHSS 2012)

The evaluation of existing RfDs, ATSDR toxicological reference values, and the derivation of the alternative scientifically defensible RfDs are described below.

Brief Summary of Existing Screening Values for Sulfolane

Three animal studies are available for consideration in deriving toxicological screening values for sulfolane. Huntingdon Life Sciences (HLS 2001) was a fully documented 90-day oral drinking water study in CD rats that was performed in accordance with Good Laboratory Practices (GLP) with detailed information on each animal. Ministry of Health and Welfare Japan (MHWJ 1999) was a 50-day oral gavage study in Crj:CD(S-D) rats as summarized in OECD (2004). Zhu, et al. (1987) was a 180-day unspecified oral study in unspecified guinea pigs. The results of Zhu, et al. (1987) were published in Chinese in a non peer-reviewed journal with little documentation.

The Canadian Council of Ministers of the Environment (CCME 2006) rejected the Zhu, et al. (1987) study on the basis of study quality and derived a screening value of 0.01 mg/kg-day based on the NOAEL for decreases in white blood cells in rats in the HLS (2001) study, which was 2.9 mg/kg/day, as the Point of Departure. CCME (2006) used a composite Uncertainty Factor of 300 (*i.e.,* Interspecies-10; intraspecies-10; 3 to account for possible teratogenic response at very high doses, subchronic to chronic exposures, and an adequate, but not extensive dataset).

Despite issues of quality, the ATSDR chose the Zhu, et al. (1987) study in its *Health Consultation* for sulfolane as the critical study because it gave a lower Point of Departure than the HLS (2001) study (ATSDR 2011). The ATSDR (2011) derived a screening value of 0.002 mg/kg-day. The Point of Departure was 1.5 mg/kg-day based on benchmark dose modeling of shrinkage of spleen white pulp in guinea pigs as the critical endpoint. The ATSDR (2011) used a composite Uncertainty Factor of 1,000 (*i.e.,* Interspecies-10; intraspecies-10; subchronic-chronic exposure duration-10). Note that the ATSDR (2010) concluded that the Zhu, et al. (1987) six-month duration study (180 day) was a *longer term* duration study that required no subchronic to chronic uncertainty factor, but in 2011, the ATSDR decided, instead, that this 180-day duration study was a *subchronic* duration study that required a subchronic to chronic

uncertainty factor. This decision does not conform to ATSDR's definition of subchronic animal studies, which are studies performed in animals for 30-90 days (ATSDR 2005).

In an update to its March 9, 2011 toxicity factor documentation for sulfolane, the Texas Commission on Environmental Quality (TCEQ 2011a) reviewed screening values presented by ToxStrategies, Inc. (ToxStrategies) and URS Corporation (URS) in a September 6, 2011 document and adopted a screening value of 0.01 mg/kg-day based on a Point of Departure defined as the lower confidence limit on the benchmark dose (BMDL) of 16.1 mg/kg-day based on decreases in white blood cell counts in rats in HLS (2001). The Point of Departure of 16.1 mg/kg-day in rats was first converted to a Human Equivalent Dose (HED) of 3.9 mg/kg-day per USEPA (2011) and TCEQ (2011b). TCEQ (2011a) then used a composite Uncertainty Factor of 300 (*i.e.*, Intraspecies- 10; subchronic to chronic exposures-10; database uncertainty- 3).

In its *Provisional Peer-Reviewed Toxicity Values for Sulfolane (CASRN 126-33-0)*, USEPA (2012a) rejected the Zhu, et al (1987) study on the basis of study quality and derived a Provisional Peer-Reviewed Toxicity Value (PPRTV) of 0.001 mg/kg-day based on the NOAEL for decreases in white blood cells in rats in HLS (2001), which was 2.9 mg/kg/day. They used a composite Uncertainty Factor of 3,000 (*i.e.,* Interspecies-10; intraspecies-10; subchronic to chronic exposures-10; database uncertainty- 3). EPA (2012a) did not use benchmark dose modeling or calculate a HED.

Scientific Critique of Existing Screening Values for Sulfolane

ARCADIS reviewed the existing screening values for sulfolane and determine which value was the most scientifically defensible. ARCADIS finds that the Zhu, et al. (1987) study fails to meet the criteria for an acceptable study established by USEPA, other governmental and nongovernmental bodies, and the Federal Information Quality Act (IQA).

Zhu et al. (1987) was a six-page report published in a Chinese journal entitled Huaxi yike daxue xuebao, (Journal of West China University of Medical Sciences). This journal no longer exists and was subsumed in 2000 by the Journal of Sichuan University (Medical Science Edition). According to OriProbe Information Sciences (2012), the main object of this journal was to present medical and health work performed by students and teachers of the university. There is no evidence on the University's website that this journal is peer-reviewed. Regardless of its peer review status, the report presents an abstract level report of a study with no supporting details.

For instance, the source and purity of the test compound and the analysis of the dosing media were not revealed. The source and strain of animals was not presented. The mode of dosing was not presented, such as drinking water, diet or gavage. It is presumed by ATSDR that the doses were given by gavage, but this most critical of information is not presented in the document. Body weights and water and food consumption were not reported, and no methods for any tests were identified. Most importantly, no individual animal data were presented, and no statistical tests were performed on the white blood cell critical endpoints.

The Zhu et al. (1987) study clearly did not meet the criteria set forth by the USEPA for study selection when deriving RfDs. USEPA's (1994) *Criteria For Assessing The Quality Of Individual Laboratory Animal Toxicity Studies* provides criteria that define the minimum information that must be reported in a study chosen as a critical study for a RfD.

In addition, the Zhu, et al (1987) study does not adhere to the standards of the IQA(Public Law 106-554; H.R. 5658), which requires the Office of Management and Budget (OMB) to issue federal agency-wide guidelines that "provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies" (Federal Register, Vol. 67, No. 38, February 22, 2002). OMB issued guidelines directing federal agencies, among other things, to: "Issue guidelines ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by the agency, ..."

In response, the USEPA developed *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* (EPA 2002b). In these guidelines, the USEPA expresses a preference for peer-reviewed scientific information as the basis

for human health risk assessment, but the USEPA concedes that not all information available for decision making is peer-reviewed. In that case, the USEPA states that the data must be performed in accordance with an accepted test protocols and Good Laboratory Practices (GLP) so that USEPA scientists can ensure that the study was properly conducted. Zhu, et al. (1987) was not peer reviewed, was not performed in accordance with a standard test guideline, was not performed GLP, nor does it contain sufficient detailed information for any reviewer to ensure that the data are valid.

In 2003, the USEPA also issued *A Summary of General Assessment Factors for Evaluating the Quality of Scientific and Technical Information* (USEPA 2003). This document also clearly demonstrates that the USEPA does not rely on studies that have insufficient information for independent review and validation.

Accordingly, the ATSDR (2011) screening criterion cannot be considered to be scientifically defensible, because it is based on the inadequately documented study by Zhu, et al. (1987), which does not conform to USEPA regulations and the IQA. In addition, the USEPA rejected the Zhu, et al. (1987) study as a critical study when deriving PPRTVs (USEPA 2012a).

The screening criteria derived by CCME (2006), TCEQ (2011a) and USEPA (2012a) are all based on the HLS (2001) study. The HLS (2001) study was performed in accordance with GLP criteria. In addition, the HLS (2001) report was a thorough and comprehensive 600 page report with a detailed protocol, a certificate of analysis of the test article, a formulation chemistry report, individual animal signs, body weights, food consumption, and water consumption, individual animal values for ophthalmoscopy, functional observation battery, hematology, blood chemistry, organ weights, macropathology observations and hisopathology observations. The USEPA also sanctioned a peer review of the HLS study, using an independent panel. The screening criteria derived from the HLS (2001) study, thus, deserve due consideration. ARCADIS finds, however, that the values from all three sources (CCME (2006), TCEQ (2011a) and EPA (2012a)), have scientific limitations that do not allow any one of the values to be endorsed.

The CCME (2006) value was based on a simple NOAEL and does not take full advantage of the benchmark dose modeling approach now favored in the United States for derivation of toxicological reference values for human health risk assessment (USEPA 2000).

The TCEQ (2011a) value was based on a value derived by ToxStrategies (2010) with an error corrected in the standard deviation of the white blood cell counts in the female highest dose group. ARCADIS performed benchmark dose modeling and confirmed that the corrected BMDL from the linear model for this endpoint is, indeed, 16.1 mg/kg-day and not 15.1 mg/kg-day as initially stated by ToxStrategies (2010). ToxStrategies (2010) found acceptable and identical model fits for four models (*i.e.*, Exponential M2, exponential M4, linear and power) and chose the results of the linear model, stating that this model was simpler than the other models, citing a USEPA precedent for reliance on the most "parsimonious" model.

ATDSR (2011), however, criticized this decision and stated that when logarithmic dose transformation is performed, the linear and exponential models are equally "parsimonious." ATSDR (2011) further stated: "When the BMDLs are within a factor of three, the lowest AIC [Akaike's Information Criterion] is chosen. Or, if multiple values have the same AIC, then an average is recommended (USEPA 2000)." ARCADIS confirmed that the USEPA's guidance (USEPA 2000) *does* state that it is recommended that the average of BMDL values be taken when multiple models adequately fit the experimental data and multiple BMDLs are within a factor of 3. On the other hand, USEPA (2000) further states that for models "that have met the default statistical criteria for adequacy and visually fit the data, any of them theoretically could be used for determining the BMDL." Thus, ToxStrategies (2010) was not deviating from USEPA (2000) guidance by choosing the linear model over the exponential models. However, the recommendation in USEPA's (2000) guidance is that BMDLs from multiple models with adequate fits can be averaged. Furthermore, a more recent presentation from USEPA stated that BMDLs *can be averaged* in such circumstances, which indicates that EPA is not explictly requiring an averaging approach.

ARCADIS notes that ATSDR (2011) has made several errors when it stated in Tables B-4, B-5, B-6, and B-7 that a particular model was the "best fitting model." In fact, all of the listed models have adequate fits to the experimental data, and in most cases the model fits are *identical*. For instance, the white blood cell data using historical controls provided BMDLs ranging from 5.54 to 16.12 mg/kg-day, and all five models (exponential M2, exponential M4, linear, power and polynomial) gave identical homogeneity variance p-values, goodness of fit p-values, and AIC values. Further, even though all four models met the scaled residual criterion of absolute value <2, the scaled residuals for the linear, power, and polynomial models showed a slightly better fit to the data than the two exponential models (M2 and M4).

ToxStrategies (2010) based its screening value on the white blood cell decrements as a critical endpoint. ARCADIS confirmed that benchmark dose modeling of decrements in lymphocytes yields slightly higher BMDLs. ARCADIS verified the white blood cell benchmark dose modeling of ToxStrategies (2011), specifically, the female rat BMDL values for the white blood cell decrements using the historical control variance are 8.78, 5.55, 16.12 and 16.12 mg/kg-day, for each of 4 BMD model types, with an average BMDL of 11.64 mg/kg-day. All models are acceptable fits to the experimental data, and the AIC values for the four models are identical. Thus, the USEPA's default averaging approach is appropriate for setting a Point of Departure.

The female rat BMDL values for the lymphocyte decrements using the historical control variance are 7.94, 4.37, 15.95, 15.95 and 15.95 mg/kg-day, for each of 5 BMD model types, with an average BMDL of 12.03 mg/kg-day. All five models (including the polynomial model) are acceptable fits to the experimental data. The AIC values for the five models are 102.5, 102.5, 102.6, 102.6, and 102.6. According to USEPA's Benchmark Dose Software manual (EPA 2012b), one model is preferred over another only if "the AIC value is substantially smaller for one model." Clearly, 102.5 is not "substantially smaller" than 102.6, so these AICs are virtually identical. Thus, USEPA's default averaging approach is appropriate for setting a Point of Departure. To summarize, the four model average Point of Departure based on white blood cell

decrements is 11.64 mg/kg-day and the five model average Point of Departure based on lymphocyte decrements is 12.03 mg/kg-day.

The USEPA (2012a) value was based on a simple NOAEL and does not take full advantage of the benchmark dose modeling approach now favored in the United States (USEPA 2000) for derivation of toxicological reference values for human health risk assessment. The USEPA (2012a) performed some initial benchmark dose modeling without log transforming the data as did ToxStrategies (2011) and ATSDR (2011). Without log transforming the data, acceptable model fits were not attained. This outcome was already reported by others, and it is unclear why the USEPA presented the unsuccessful benchmark dose modeling efforts and then did not proceed to log transform the data as did others.

ARCADIS investigated the scientific appropriateness of log transforming data during benchmark dose modeling. Log transformation of the data is explicitly allowed by USEPA guidance (USEPA 1995; 2000; 2012a,b,c). For instance, USEPA (1995) states: "...it may be necessary to transform continuous data in some cases so that they better satisfy the assumptions of a normal distribution. A log-transform is often used for this purpose." Similarly, when discussing acceptable adjustments to the data in the Benchmark Dose (BMD) Methodology Software Tutorial, USEPA (2012c) states: "In certain cases, the typical models for a standard study design cannot be used with the observed data as, for example, when the data are not monotonic, or when the response rises abruptly after some lower doses that give only the background response. In these cases, adjustments to the data (e.g., a log-transformation of dose) or the model (e.g., adjustments for unrelated deaths) may be necessary."

More importantly, the USEPA itself has log transformed data sets when performing benchmark dose modeling. In the IRIS profile for benzene for instance, USEPA (2012d) states: "Most of the data were supralinear (i.e., the magnitude of the reductions in lymphocyte count decreased with increasing unit dose), and it was necessary to transform the dose data according to the formula d' = ln(d+1) in order to fit the available models." This regulatory precedent for log dose transformation concerns a data set that matches the data set for sulfolane. In both cases, the critical effect was decreased white blood cell counts, and in both cases simple log transformation of the raw data provided acceptable model fits.

In addition, ARCADIS reviewed the USEPA's database of Provisional Peer-Reviewed Toxicity Values (PPRTVs) and found that USEPA has derived a total of 44 chronic oral RfDs and 33 chronic reference concentrations. Of the 77 total noncancer toxicity values, 26 are based on benchmark dose modeled values (~33%) with 9 of the 26 (35%) based on a lognormal transformation of the dose-response data from the critical study.

Lastly, log dose transformation is performed in peer-reviewed scientific studies in which reference doses and reference concentrations were derived by benchmark dose modeling of data of critical effects (TERA 2005; Budtz-Jorgensen et al., 2000; Grandjean et al. 1997; Suwazono et al. 2006, 2011; Gaylor et al. 1998; Clewell et al. 2003).

Derivation of Alternative Reference Doses

Based on the above logic, a scientifically defensible approach to deriving chronic and subchronic RfDs for sulfolane is as follows:

1. Based on a quality assessment, the HLS (2001) is defined as the critical study (USEPA, 1994, 2002a, 2002b, 2003, 2012a; Klimisch et al. 1997).

2. The HLS (2001) data are subjected to benchmark dose modeling to define the $BMDL_{10}$ per USEPA guidance (USEPA, 1995, 2000, 2002, 2012a,b).

3. Benchmark dose modeling is performed using log transformed doses per USEPA guidance (USEPA, 1995, 2000, 2012a,b,c;) and in accordance with USEPA's RfC for benzene (USEPA, 2012d). The appropriateness of log transformation of doses is supported by peer-reviewed literature citations (TERA, 2005; Budtz-Jorgensen et al. 2000; Grandjean et al., 1997; Suwazono et al., 2006, 2011; Gaylor et al., 1998; Clewell et al., 2003).

4. Benchmark dose modeling is performed using historical control variances per USEPA guidance (USEPA 1994; 2000 2012b).

5. White blood cell reduction is defined as the critical endpoint instead of lymphocyte reduction because benchmark dose modeling of white blood cell data results in slightly lower BMDLs. USEPA (2012a), TCEQ (2011a), and CCME (2006) all based their screening criteria on decreases in white blood cells in rats as reported by HLS (2001).

6. Because the exponential M2, exponential M4, linear, and power models all provide acceptable fits to the experimental data and because no model has a "substantially lower" AIC value, EPA's default approach of averaging the BMDLs and designating the four model average BMDL as the Point of Departure is used (EPA 2000).

7. The four model average BMDL is 11.64 mg/kg-day for white blood cells (12.03 mg/kg-day for lymphocytes). Thus, the Point of Departure is defined as 11.64 mg/kg-day.

8. The chronic RfD is derived from the Point of Departure using a standard composite Uncertainty Factor of 1,000 (Interspecies-10; intraspecies-10; subchronic to chronic exposures-10).

The interspecies UF of 10 is a standard UF unless one converts the animal dose to a Human Equivalent Dose (HED). In that case, the HED conversion is considered by EPA to comprise the pharmacokinetic portion of the interspecies UF, and only the pharmacodynamic portion of that UF is used (1-3). In this case, the standard UF of 10 is used to be consistent with the approaches taken by EPA (2012a), ATSDR

(2011), and CCME (2006). If the HED were calculated and then the maximum pharmacodynamic UF of 3 applied, the total effect would be to reduce the chronic RfD from 0.012 to 0.01 and the subchronic RfD from 0.12 to 0.1 mg/kg-day. TCEQ (2011a) used an interspecies UF of 1 after converting the animal dose to an HED.

The intraspecies UF of 10 is a standard UF used by USEPA (2012a), ATSDR (2011), CCME (2006) and TCEQ (2011a).

The subchronic to chronic UF of 10 is a standard UF used by USEPA (2012a), ATSDR (2011), CCME (2006) and TCEQ (2011a).

Because the database is adequate for setting RfDs, a database uncertainty factor of 1 was used.

The composite UF of 1,000 is the same composite UF as used by ATSDR (2011). It is higher than the composite UFs of TCEQ (2011a) and CCME (2006), which were both 300. Lastly, is it slightly lower than the composite UF used by USEPA (2012a). Thus, the composite UF is within the range of UFs used by others.

9. The subchronic RfD is derived from the Point of Departure using a standard composite Uncertainty Factor of 100 (Interspecies-10; intraspecies-10). The subchronic RfD is 0.12 mg/kg-day, rounded to 0.1 mg/kg-day. The UFs are as noted above with the omission of the subchronic to chronic UF, which is unnecessary for subchronic exposures.

10. The chronic RfD is 0.012 mg/kg-day, rounded to 0.01 mg/kg-day.

11. The chronic RfD is virtually identical to the TCEQ (2011a) value (0.013 mg/kg-day) and the CCME (2006) value (0.010 mg/kg-day), although the values are derived using different approaches.

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Appendix I

Adult Lead Model Spreadsheet – Calculations of Blood Lead Concentrations